REMARKS

I. OBJECTIONS TO THE SPECIFICATION

The Examiner objected to the title of the specification as allegedly it was not descriptive of the claimed invention. The amended title is more descriptive. Thus, the objection to the specification should be withdrawn.

II. WITHDRAWAL OF CLAIM 62 AND THE RESTRICTION REQUIREMENT IN GENERAL ARE IMPROPER

The Applicants maintain their traversal for all reasons already of record. The Examiner continues to assert, for purposes of *restriction*) that the claims are drawn to differences (polymorphisms in the FLAP gene) rather than to common structural features; or drawn to "the FLAP gene"; or drawn to "variants of the FLAP gene". (Office action at p. 3.) The claims are drawn to none of these things. Rather, the PTO's characterization at page 5 (for purposes of *examination*) is closer to being accurate – that the claims are drawn to a method of assessing susceptibility to MI.

Claim 62 specifies all of the limitations of claim 61 and further specifies assessing one additional polymorphic site. It is improper to withdraw from consideration a dependent claim that includes all of the limitations of claim 61, currently under examination. The Applicants acknowledge the notation in an earlier action that combinations containing allowable polymorphisms will be rejoined in the future, but it is improper to withdraw such claims from examination to begin with. Examination would progress more expeditiously by concurrent examination of claim 62 to resolve all patentability issues.

III. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, ALLEGING LACK OF ENABLEMENT SHOULD BE WITHDRAWN

The Patent Office rejected claims 61, 65 and 66 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. The Examiner repeated the basis for the enablement rejection from the previous office action. In particular, the Examiner based the rejection on the conclusion that the art is highly unpredictable and

there is allegedly no clear association between polymorphisms of the FLAP gene and a disorder; and therefore, the claims allegedly cannot be practiced without further requiring unpredictable and undue experimentation. Applicants continue to traverse this rejection and repeat by reference arguments made in their previous submissions. In addition, the Applicants submit herewith a Declaration of Gudmar Thorleifsson Under 37 C.F.R. § 1.132 (referred to herein as the "Thorleifsson Declaration") that addresses certain specific issues or questions raised by the Examiner.

A. Response to general issues raised in the Office action.

1. Nature of the invention and breadth of the claims

In the first paragraph on page 5 of the action, the Examiner acknowledges that claims 61 and dependent claims are drawn to a method specifying assessing a haplotype defined by specifically enumerated polymorphisms. Then, for no understandable reason, the Examiner concludes in the very next paragraph, "The nature of the invention, therefore, requires knowledge of predictive associations between the haplotype in any FLAP nucleic acid and susceptibility of myocardial infarction." The proper conclusion with respect to claim 61 and dependent claims is that it requires knowledge of the predictive association of the *specified haplotype* and MI. This predictive association is taught in the application and confirmed by repeated studies, as demonstrated in Applicant's previous submissions and discussed in subpart B below. Thus, the nature of the invention and breadth of the claims dictate a conclusion that the specification enables the claims.

2. Unpredictability of the art and state of the prior art.

Notwithstanding the Examiner's suggestion to the contrary, the existing studies conclusively establish the susceptibility risk between the haplotype recited in claim 61 and MI. (See discussion in subpart B below and the declaration filed herewith. A conclusion that the claims are enabled is required.

The large amount of available data for the FLAP haplotype and MI make any consideration of other references, that discuss other genetic associations, essentially irrelevant.

3. Guidance in the specification

Again, there is an inexplicable disconnect between the subject matter recited in the claims, and the Patent Office's analysis of the specification. The Patent Office discusses data in the specification relating to 49 individual markers, and concludes (solely from this data) that the specification only amounts to an invitation to experiment. The specification also contains haplotype data, and the current claims specify analysis of a multi-marker haplotype that is shown in the application and in subsequent studies to correlate with increased susceptibility to MI. This factor, too, requires a conclusion that the specification is enabling.

4. Quantity of Experimentation

No experimentation is required to practice the invention as presently claimed. This factor, too, requires a conclusion that the claims are enabled. The application teaches how to measure the specified haplotype, and teaches the conclusion to draw from its absence or its presence in an individual.

The Patent Office asserts that "the claims have been amended to read that 'the absence of the haplotype identified the individual as not have the elevated susceptibility to MI.'" This quotation is inaccurate because it is incomplete. The amended claims specify "wherein the absence of the haplotype in the nucleic acid of the individual identifies the individual as not having the elevated susceptibility to MI *due to the haplotype*."

The Patent Office asserted that the cropped clause at issue is inaccurate because a person could have one of the *other haplotypes taught in the application as conferring susceptibility to MI.* "Thus, the absence of the recited haplotype does not identify the individual as not having the elevated susceptibility to MI."

At the outset, the Patent Office's analysis demonstrates the absurdity of the restriction requirement. The Patent Office asserts, for purposes of restriction, that because all haplotypes are different, it is only willing to examine claims that specify a single haplotype. Then, for purposes of examination, the Patent Office asserts that claims that specify the elected haplotype are incomplete because they fail to address the predictive value of other haplotypes – that the Patent Office has refused to examine!

To address this Catch-22 situation, the Applicants previously amended the claims to specify "wherein the absence of the haplotype in the nucleic acid of the individual identifies the individual as not having the elevated susceptibility to MI *due to the haplotype*." The words "the haplotype" refer to the screened-for haplotype. This is a completely accurate conclusion to draw from the method claim that the Patent Office is willing to examine. The conclusion that is drawn is that the human individual does (or does not) have the susceptibility that is correlative to the haplotype tested. The individual may or may not have susceptibility due to other haplotypes, or obesity, or diabetes, or other conditions or genetics that are not the subject of the method.

The Patent Office's questions relating to ethnicity as it relates to the predictive value of the haplotype are further addressed below in subpart B.

5. Level of skill

The Patent Office acknowledges that the level of skill in the art is high, which weighs in favor of a conclusion that the application is enabling.

B. Response to Patent Office's analysis of Applicant's declarations and arguments.

1. Differences in the Data

The Examiner stated that the Declaration of Andrei Manolescu (referred to herein as the "Manolescu Declaration"), submitted in response to the previous office action was not persuasive. The Examiner maintained the enablement rejection because the record is allegedly unclear as the Manolescu Declaration, the Helgadottir Declaration and the table presented for interview purposes appear to differ.

One difference between the declarations and the interview table was the P-values provided in each. The Applicants remind the Examiner that the interview table was presented for illustrative purposes during the interview, was not a completed or signed declaration, and was not intended for entry into the file as an official submission. Second, as explained in the Thorleifsson Declaration, the table presented in the interview reported two-sided P-values, while the Manolescu Declaration and the Helgadottir Declaration report one-sided P-values. After adjusting for this difference in statistical analysis, the P-values in the

interview table would agree with the table provided in the Manolescu Declaration. (See ¶ 13 of the Thorleifsson Declaration).

The Examiner also pointed out that the studies described in the declaration and the interview table had varying numbers of subjects. Paragraphs 14-19 of the Thorleifsson Declaration indicate that the analyses presented in the Manolescu Declaration and Helgadottir Declaration were carried out at different time points and each study was carried out with the most recent phenotype data available at the time, and this data differed slightly for the two declarations. For example, subsequent to the completion of the analysis described in the Helgadottir Declaration, three controls were determined to have coronary heart disease and were excluded from the analysis described in the Manolescu Declaration. (See ¶15 of the Thorleifsson Declaration). There were five additional subjects reporting MI in the Cleveland cohort analyzed for the Manolescu Declaration, and three of these subjects were considered controls in the analysis described in the Helgadottir Declaration. (See ¶16 if the Thorleifsson Declaration). Similarly, updated phenotype information on cardiovascular disease history resulted in disqualification of several control subjects of the Atlanta cohort prior to the analysis described in the Manolescu Declaration. (See ¶17 of the Thorleifsson Declaration). Furthermore, additional genotyping analysis led to the addition of subjects in the Atlanta and Durham cohorts for the analysis described in the Manolescu Declaration. (See ¶ 17 & 18 of the Thorleifsson Declaration.)

Thus, there are valid reasons as to why the numbers of subject analyzed differed in the studies described in the Manolescu Declaration and the Helgadottir Declaration. Even though the differences in the datasets resulted in different numerical calculations, the conclusion about the correlation to be drawn from each analysis was the same, and remained statistically significant.

2. Ethnicity

The Examiner maintained that ethnic or "inter-ethnic" variability confer different risk for MI and the skilled artisan allegedly would not be able to assess susceptibility to MI in different populations using the claimed invention. As stated in the response to the previous office action and acknowledged by the Examiner in the present

Office Action (see p. 11), ethnic variability does not give rise to questions of statutory enablement for the present claims. Statutory enablement involves whether an application describes an invention in a manner that allows those of ordinary skill to practice the invention.

The Examiner alleges that the skilled artisan cannot carry out the broadly claimed invention without undue experimentation. However, the claims are directed to screening for a specific haplotype and the present application teaches a person of ordinary skill how to perform the haplotype screen *without regard to ethnicity*, and teaches the conclusion that can reasonably be drawn from it based on population genetics. As with other correlation tests, the results provide helpful information for medical treatment or lifestyle management, and are indicative of risk at the population level. The present invention is appropriately claimed insofar as an individual is assessed for one type of data (FLAP haplotype) and a conclusion about susceptibility (supported by statistically validated data) is drawn based on the FLAP haplotype assessment only. The conclusion does not require ethnicity data.

As stated in the previous response, human variability is the rule, not the exception, for all aspects of medicine, including diagnostic tests based on biochemistry; safety of drugs; efficacy of drugs; susceptibility to diseases; life expectancy, and so on. While it may be possible or desirable to refine any medical test or treatment or other medical procedure to an ethnicity or sub-ethnicity, that is not the current state of medicine and is not part of the statutory requirement of enablement for a claim that does not require a conclusion based on ethnicity. Ethnicity itself is defined according to arbitrary geographical and/or physical appearance criteria, which may or may not translate into genetic differences. (Genetic variability exists within particular ethnic groups which may be comparable to genetic differences between ethnicities.) The Applicants previous amendment cited many examples of diagnostic tests that are considered medically useful, even though their predictive value with respect to any particular person is not considered a certainty. The data in the application and the larger meta-analysis show that the test is valid and useful and provides another tool for assessing risk for MI

Moreover, most of the Examiner's concerns as to the possible effects of "ethnicity" may actually be attributable to the low power of certain individual studies (discussed in the next subpart). In this regard, it is important to note that the Zee study, the UK study, and the Italy study cited by the Examiner in the discussion of ethnicity all revealed data supportive of the conclusion of increased susceptibility, even though the sample size may have been too small to rise to the level of statistical significance. The meta-analysis, with all ethnicities combined, revealed a statistically significant correlation between the haplotype and increased susceptibility to MI.

3. Relative Risk of "Three or More" is NOT a suitable Threshold

Despite the evidence provided in the Helgadottir and Manolescu Declaration, the Examiner cited to a passage in Ioannidis *et al.* purportedly relating to what editors look for in a scientific manuscript for publication, and maintained the view that a relative risk (RR) of three or more is needed for a risk to represent a significant result, worthy of patent protection. The Thorleifsson Declaration provides evidence that RR > 3 does not represent the accepted threshold criteria for the publication of genetic association studies. In fact, many important genetic correlations behave like the correlation in the present application, with a much lower, but statistically significant, relative risk.

The Thorleifsson Declaration explains in detail the concept of statistical power in genetic studies and why it is important for understanding genetic association studies. Briefly, the Thorleifsson Declaration describes that for genetic variants that have a small effect, a large cohort size is necessary to detect a statistically significant association between the variant and risk for a disease state. Statistical power is the probability of finding a statistically significant difference between cases and controls in a particular study, given a real underlying difference between cases and controls. The power of a genetic association study depends on several factors, most important being the size of the study populations (*e.g.*, cohort size; numbers of cases and controls), but also the effect size or the odds ratio (OR) of the genetic variant and the frequency of the variants. "Odds ratio" is a measure of effect size; it can be defined as the ratio of the odds of an event occurring in one group to the odds of it occurring in another group. An odds ratio of 1 implies that the event is equally likely in both groups. When an odds ratio is greater than 1 when comparing cases to controls, it implies that a particular variant is more likely to be found in the case group than in the controls. The

power of an association study increases both with increased cohort size and larger OR of the variant. (See ¶5 of the Thorleifsson Declaration).

The Thorleifsson Declaration identifies a number of peer-reviewed, published studies in which the risk conferred was relatively small; however, these studies meet the established criteria for statistical significance. (See ¶ 6 of the Thorleifsson Declaration). These exemplary studies are large multi-center Genome-Wide Association studies. Recently, many genetic variants that correlate with risk for common diseases have been identified, and the identification of these variants have established in the art that genetic risk for common disease appears to be modulated through multiple, small relative risk variants, and these variants work in a concerted manner in any given individual along with environmental risk factors to establish an overall predisposition for a particular disease. (See ¶ 8 of the Thorleifsson Declaration.) Because these small relative risk markers are statistically valid and provide useful medical information, it is improper to require for patentability an arbitrarily large relative risk for a genetic variant. A valid association is established by well designed studies with sufficient power to demonstrate that an observed association between a variant and a disease is statistically significant. That is precisely the situation here.

In addition, the Examiner continues to doubt the significance of the association of genetic variants and MI of the invention, including the data provided in the Helgadottir and Manolescu Declarations because the relative risk scores are low and the P-values are high. As described in detail in the Thorleifsson Declaration and above, the results from multiple studies were combined and analyzed using a standard meta-analysis. This analysis allows for analysis of a large sample size which is valuable to achieve acceptable statistical power when the genetic effects on phenotype are small, *e.g.* low relative risks. (See ¶12 of the Declaration). Therefore, while individual studies may not yield significant results, the combined results in such meta-analysis can be very significant if there is consistency in the direction of the observed effect across the studies in the analysis.[1] Therefore, as demonstrated in the Helgadottir and Manolescu Declarations, a conclusion of enablement is

[1] To provide a crude analogy, if a coin were flipped four times and "heads" appeared three times ("tails" once), the 75% occurrence of heads would reasonably attributed to sampling variation. Six heads in ten flips (60%) would reasonably generate the same conclusion. If, however, there were 55 million heads after 100 million flips (55%), the reasonable conclusion to be drawn from statistics is that the coin was not true, and was instead weighted to favor "heads."

appropriate in view of the fact that the incremental risk for MI associated with FLAP HapA, though not nearly as high as 3.0, has been shown through large studies and meta-analysis of multiple studies to be statistically significant, and not an artifact of a small study.

C. Conclusion

In view of the above comments and the evidence provided in the Thorleifsson Declaration, in addition to the evidence provided in the previously filed declarations, the claims are enabled by the specification. Therefore, the rejection under 35 U.S.C. § 112, first paragraph should be withdrawn.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance, and early notice thereof is requested.

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